33929 - Answering Reviewers

Name of journal: World Journal of Hepatology
Manuscript NO: 33929
Title: Improved Hepascore in Hepatitis C predicts reversal in risk of adverse outcome

Dear editor and peer reviewers,

Thank you for giving us the opportunity to submit a revised version of our manuscript. We would also like to thank the reviewers for their helpful comments. We have considered each of these comments individually and have incorporated the appropriate changes in the revised version of the manuscript. We believe that this revision addresses the reviewer comments.

Answers to reviewers' questions

Reviewer's code: 00033049
Reviewer's country: United States

1. Study population: the median Hepascore was 0.48 with range of 0.02 to 1.0. According to the original articles on Hepascore, majority of the subjects would have significant fibrosis. However, there was no detail on the distribution of the study population. For example, how many has cirrhosis by Hepascore and/or clinically? How many patients is in each quartile as defined by the authors (Figure 1)? Readers need to know more about the distribution in order to interpret the findings.

The distribution of the severity of liver fibrosis in the study population has been added to the manuscript on page 9, paragraph 2. 129 (37%) had a Hepascore ≤0.25, 73 (21%) had a Hepascore from 0.26 to 0.5, 43 (12%) had a Hepascore from 0.51 to 0.75 and 100 (29%) had a Hepascore >0.75. Patients with a Hepascore >0.75 are considered to have severe (F3 or F4) fibrosis.

2. *According to table 1, 38 patients achieved SVR. This complicated the interpretation since achieving SVR had been shown to change the natural history and reduced risk of HCC. It was also not clear how many were treated but did not achieve SVR. Should show additional data on the treated vs untreated group. This is particularly important with regard to HCC (as one of the endpoints).*

A sensitivity analysis was performed for patients with a SVR and exclusion of these patients had no significant effect on the model or outcomes. This result is found on Page 10, paragraph 1. Patients with a SVR are still at risk of developing adverse clinical outcomes as 4 patients with SVR reached an endpoint. An analysis of treated patients vs. untreated patients was not performed.

3. What was the relationship, if any, between changes in Hepascore over time and variable such as HCV treatment, elements of metabolic syndrome (e.g. BMI), alcohol consumption? Alcohol use can increase the GGTP which is one of the variables in Hepascore.

Data on alcohol use and BMI were not available for analysis. See response for question 2 regarding HCV treatment. The lack of data on BMI and alcohol consumption was identified as a potential limitation of the study and this prevents sub-group analysis. This was discussed in the original submission (Page 12, paragraph 2). However, delta Hepascore measures overall change in clinical outcome risk and is not reliant on a single factor.

4. The primary endpoint is liver related death or liver transplant. According to table 1, it was 28. However, there was only 8 LRD, so does it mean that 20 received liver transplant? There were 16 decompensation and 15 HCC, does it also mean patients had multiple events (i.e. LD and HCC)?

LRD includes those who died from liver disease and those who had a liver transplant, see page 7, paragraph 3. Some patients had multiple outcomes. For example, they developed HCC before progressing to liver related death. The composite endpoint only considers these patients once. This was added to methods page 7, paragraph 3.

5. It would be useful to have a table summarizing the characteristics of each of the 4 quantile e.g. number of patients, mean age, ALT, platelet count.

ALT and platelet count was not available for analysis in this study. The characteristics of patients with Hepascore >0.75 has been added to Table 1.

6. Not clear why the second Hepascore was done and under what circumstance. For example, were they mostly done among those who achieved SVR looking for fibrosis regression and those whom clinician suspected clinical progression (in consideration of anti-viral therapy)? There was not enough detail about the group who had repeat Hepascore done. Also, of note, the range was very wide (0.03 to 12.5). Since fibrosis progression (assuming that is what the Hepacore is measuring) is a very slow process, should the analysis include only those with repeat Hepascore, say, more than 2 years apart? However, it looked like there might only be ~50 patients and not clear how many event occurred.

Follow-up Hepascore tests are performed routinely in the clinical management of all chronic HCV patients. This is irrespective of whether patients received anti-viral treatment or not. We agree that the time between repeat Hepascore tests is important due to the slow time of regression or progression of fibrosis. A time analysis of delta Hepascore was performed and the results were discussed on Page 10, paragraph 3 and in Figure 3. We found that the minimum time interval between Hepascore tests that resulted in useful clinical information was one year.

7. Table 2, the 95% CI for the second Hepascore was very wide (e.g. 0.0-4.6E+53), no doubt due to very small sample size. Could this be correct?

We agree that the very wide 95% CI for the second Hepascore is due to the small sample size and in addition the small range of Hepascore values from zero to one.

8. If Hepascore is truly a reliable reflection of fibrosis, only patients with advanced fibrosis (F3 or F4) is at risk for HCC, and only F4 patients are at risk for decompensating events and liver related death. Should the analysis be focusing on this group (e.g. Hepascore score >0.8) instead of the entire cohort? This is also suggested by figure 1. What is the sensitivity and specificity of Hepascore >0.75 for cirrhosis? Again, how many patients is in this category?

The analysis did focus on those patients with a high Hepascore (>0.75) in the delta Hepascore analysis. A cut point of Hepascore > 0.75 was not originally used to diagnose cirrhosis, however our previous study demonstrated that Hepascore > 0.75 was predictive of adverse clinical outcome in CHC patients. See reference 10.

9. The delta Hepascore is intrinsically fraud (?flawed). The variable that is missing is time. A 0.1 change over 1 year or over 5 years have different implication.

The aim of this paper was not to evaluate the predictive ability of the ***rate of change*** of Hepascore values. This paper analyzed the ***change*** in Hepascore (fibrosis) values. The rate of fibrosis change in each patient will not be constant and therefore the predictive ability of the rate is unknown, unlike the absolute Hepascore value.

Reviewer's code: 00009879
Reviewer's country: South Korea

10. Could you mention about HCV genotype? Could you mention about treatment modality and therapeutic response?

Please see response to reviewer 1, Qu. 2.

Answers to editor's questions

1. *When you revise back, please provide the format of doc, not the pdf. Thank you.*

Done

2. *Please highlight the changes made to the manuscript according to the peer-reviewers' comments.*

Please see the section above.

3. *Title. The title should be no more than 12 words.*

We have revised the title to: **Improved Hepascore in Hepatitis C predicts reversal in risk of adverse outcome**

4. *Running title. A short running title of no more than 6 words should be provided. It should state the topic of the paper. For example, Losurdo G et al. Two year follow-up of duodenal lymphocytosis.*

We have added a running title as follows**: Jeffrey AW et al. Hepascore in Hepatitis C**

5. *Authorship, institution, author contributions, institutional review board statement, informed consent statement, conflict-of-interest statement, data sharing statement, correspondence, telephone and fax to be added in accordance with the Format_for_Manuscript_Revision-Retrospective_Cohort_Study document.*

Done

6. *Core Tip and Citation*

Done

7. *Audio Core Tip*

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8. *Please put the reference numbers in square brackets in superscript at the end of ciatation content or after the cited author's name. Please check across the text.*

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9. *Please add PubMed citation numbers and DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI.*

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10. *Please write the COMMENTS section.*

Done